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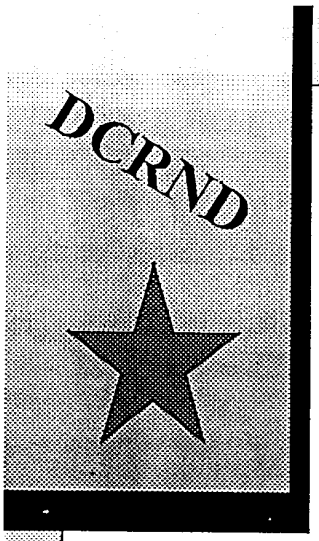

Guidance for Implantable Cardioverter Defibrillators Version 4.3 Draft Document

This guidance Document is being distributed for comment purposes only.

Office of Device Evaluation
Division of Cardiovascular, Respiratory and Neurological Devices

Draft released for comment on: June 24, 1996

Comments and suggestions regarding this draft document should be submitted within 30 days of the above release date to Dan Spyker, DXS @FDADR.CDRH.FDA.GOV, or FAX (301) 594-3076. Comments and suggestions received after this date may not be acted upon by the Agency until the document is next revised or updated. For questions regarding this draft document, contact Dan Spyker at (301) 443-8320.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Devices and Radiological Health

DRAFT Guidance for
Implantable Cardioverter-Defibrillators

Version 4.3

June 19, 1996

Center for Devices and Radiological Health

Food and Drug Administration

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Numbers in square brackets [##] appearing in this guidance refer to citations in the Bibliography (Section V)

Table of Contents

I. Overview

A. Introduction

The automatic implantable pacer cardioverter defibrillator (ICD) is an electronic device designed to monitor the heart rhythm, detect tachyarrhythmias, ventricular tachycardia (VT) or ventricular fibrillation (VF), and deliver therapy in the form of anti-tachyarrhythmia pacing (ATP), cardioversion, and/or defibrillation to terminate the arrhythmia. Back-up pacing and antitachycardia pacing therapies are also available to treat episodes of bradycardia and VT respectively. In general, the device is intended for those patients who have had episodes of VT and/or VF, and who are resistant to antiarrhythmic drug therapy. All patients should undergo baseline electrophysiological (EP) testing prior to and during implantation of the device. Electrophysiological tests provide essential data which are necessary to thoroughly evaluate the patient's cardiovascular status and to determine whether the patient is a candidate for the device. The data also will assist the physician in the appropriate selection and programming of a defibrillator system.

The development, manufacture, and clinical use of automatic Implantable Cardiac Defibrillators (ICDs) have reached a maturity prompting a documentation of the agency's regulatory approach. Particular developments include:

- ICD's are being **downsized** to a weight and volume comparable to that of the first or second generation permanent pacemakers. Clinical experience with pectoral pacemaker implantation has thus become relevant to pectoral ICD implantation. As devices become smaller, the site of implant is going to be a matter of patient and/or physician preference.
- The **unipolar lead system** (can as electrode) ICD's gives a different defibrillating vector created by this lead configuration. Although defibrillator efficacy can be assessed by standard studies, the morbidity related to the tissue contact with a "hot" can may require several years to assess.
- Current generation ICD's by various manufacturers offer transvenous leads, sensing-pacing-cardioverting-defibrillating tiered therapy, bradycardia-support, self-regeneration and stored electrograms, with a conversion rate of 98+%. Very **large studies would be required** to demonstrate incremental improvement in efficacy.
- The **changes in reimbursement** policies for investigational devices may slow investigator and patient recruiting and contribute larger portions of clinical trials done outside the US.

B. Objective/Scope

The **purpose of this document** is to guide the regulatory review of ICD applications. This guidance discusses key elements reviewers look for in an ICD submission thereby providing a common baseline from which both manufacturers and scientific reviewers can operate.

Principal goals in developing this guidance are: **1) reduced development time and, 2) improved predictability of agency interaction with sponsors developing ICDs.** This can be accomplished if we are able to adjust (reduce) and articulate the requirements for ICD development and approval. The agency sought initial scientific review and public scrutiny of these recommendations at the public panel meeting 1/29/96.

ICD development and approval can be expedited if the agency can:

- apply the experience (maturity) of ICD sponsors and the agency to avoid unnecessary requirements
- take a flexible approach to regulation; i.e., suit the regulatory requirement to the change (one size doesn't fit all)
- use performance specifications and preclinical evaluation to the maximum extent possible
- use postmarket surveillance to reduce premarketing requirements, where appropriate
- reduce uncertainty by developing a sound, scientific, public strategy for ICD development and approval
- facilitate communication, especially early in the process, among the agency, the sponsors, and the panel

This guidance document describes the agency's assessment of the testing necessary for an ICD prior to implanting in humans, and our review of the information supporting market release. The guidance considers evaluation of critical components of the defibrillator system, i.e., electronic circuitry, batteries, capacitors and leads, biocompatibility testing and finished device/system testing. The guidance also explains the basis for deciding the type of application (IDE, PMA, PMA supplement) and provides information regarding preparation of the application. It provides general information pertaining to the design of clinical trials, both pre-PMA and post-PMA.

Several sponsor comments emphasized the perception that panel reviews increased approval time and effort.

- The agency will evaluate the need for panel review (and each of our regulatory requirements) in terms of the "value added to the development and approval process" for the maturing ICD technology. A panel review is proposed when the application raises a "new clinical issue" (an issue not previously reviewed by the panel)
- The agency is also committed to expediting the panel-track reviews through better planning (earlier decisions, project scheduling) and more reviewable panel packs.

C. Summary of Application Requirements

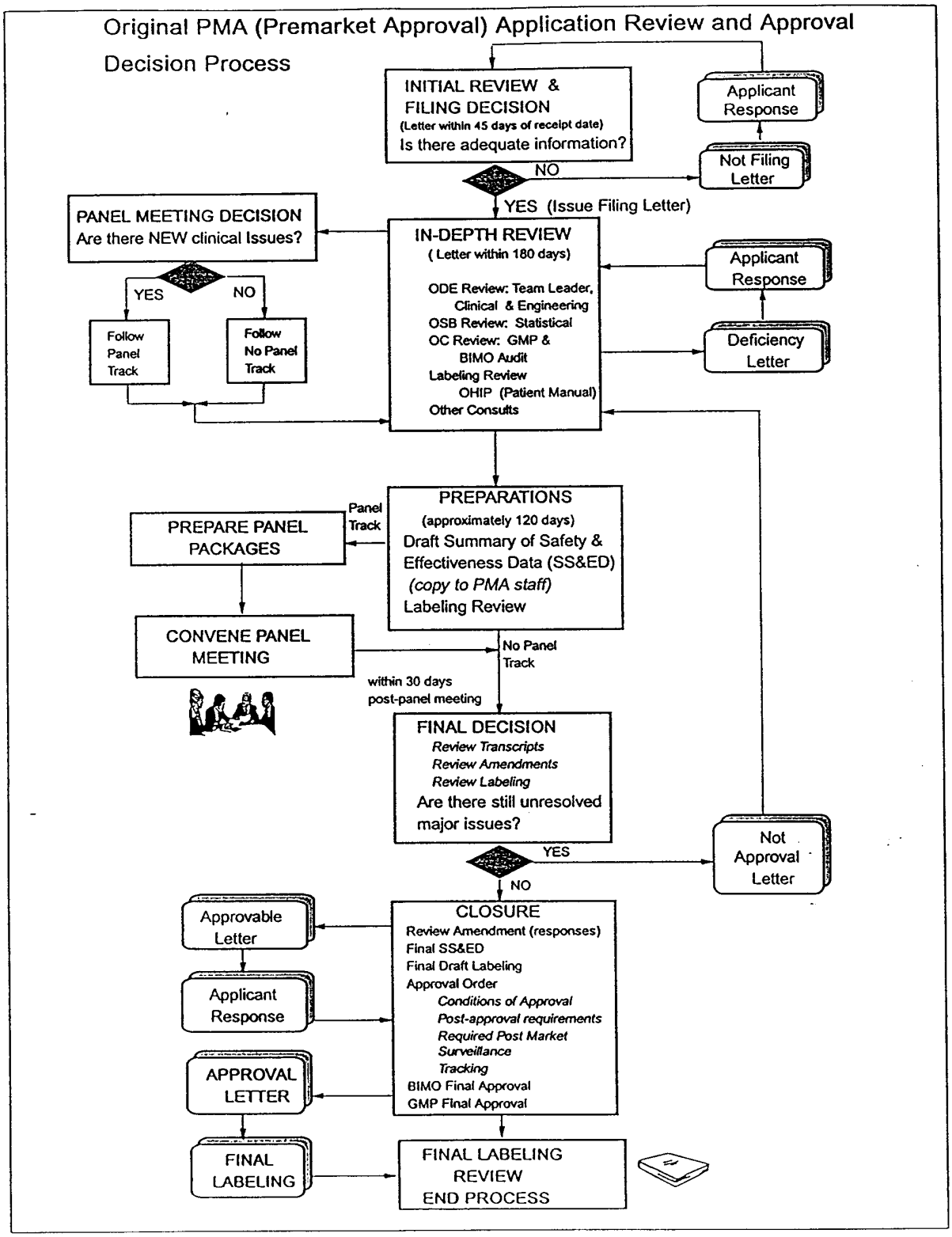
New implantable defibrillators and pacemakers are approved by the FDA through a premarket approval application (PMA) or a supplement to an already-approved PMA (PMAS). Within forty-five days of receipt date, a filing/not-filing decision is reached and a letter is sent to the sponsor (applicant). After FDA's decision to file the application, an in-depth review is conducted by a team of FDA reviewers . If the application is not filed, the sponsor will be given reasons why, with deficiencies. The sponsor should then amend the application and resubmit it for another initial review.

Development of the Summary of Safety and Effectiveness Data (SSED) and labeling continues throughout the entire process.

The review of an original PMA which raises a new clinical issue will typically include a panel review. Within 30 days of a panel meeting, FDA will make a final decision on whether to approve the application with conditions (Approvable Letter) or not approve (Not Approval Letter). The sponsor receives the final Approval Letter after acknowledgment and acceptance of the Conditions of Approval. FDA's recognition and approval of the final labeling signifies completion of the process. Figure 1 shows a schematic of the major parts of the PMA approval process.

Figure 1. PMA Approval Process

2



The application requirements (preclinical testing, clinical study, postmarket surveillance, type of application, and panel review) depend on the clinical and technology issues raised by the ICD change. Table 1 lists the requirements for six categories based on three technology categories (novel design, evolutional, and existing) and two clinical categories (whether or not clinical data will be required before PMA or PMA supplement approval).

Table 1. ICD Application Categories

Clinical Data Required	Technology Issues		
Premarketing	**Novel Design (1)**	**Evolutional (2)**	**Existing (3)**
PreClinical Testing	Bench + Animal	Bench ± Animal	Bench ± Animal
Clinical Study	Large	Medium	Small
Postmarket surveillance	Yes	Probably	Maybe
Type of Application	Original PMA	PMA Supplement	PMA Supplement
Panel Review	Yes	If first	If first
No Premarketing	**Novel Design (4)**	**Evolutional (5)**	**Existing (6)**
PreClinical Testing	Bench ± Animal	Bench	± Bench
Clinical Study	none	none	none
Postmarket surveillance	Yes	Probably	no
Type of Application	PMA Supplement	PMA Supplement	PMA annual report
Panel Review	possibly	no	no

Where changes involve more than one of the categories, the greatest data requirements (generally the lowest category number) will apply.

In Table 1, an original PMA should be submitted in the categories where a supplement or annual report is required if the device is not PMA approved.

Definitions for Table 1

Descriptions and definitions of the categories and terms used in Table 1 follow. The concepts of novel and evolutional technology were suggested by the North American Society for Pacing and Electrophysiology (NASPE) [1].

Novel Technology: This category includes any ICD pulse generator or lead system functionality which differs significantly from this sponsor's approved devices.

Evolutional Technology: This category includes design changes in (evolution of) an ICD representing an incremental change from the ICD which already has PMA approval.

Existing Technology: This category includes PMA approved devices used where the functionality is unchanged.

Premarketing Clinical Data: Sufficient valid scientific evidence should be developed to demonstrate that the ICD, as labeled, will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the ICD. Comprehensive clinical studies are generally required to develop this evidence.

No Premarketing Clinical Data: Once safety and effectiveness have been demonstrated for an ICD (PMA approved), changes which do not significantly impact clinical performance may be approached as a PMA supplement not requiring pre-approval clinical data. In some instances (Categories 4 or 5), postmarketing studies may be required.

The dimensions of a clinical study (number of patients implanted, duration of exposure, number of centers, frequency of observation) depend on the study objectives, endpoints and design. Table 1 suggests relative minimum dimensions (large, medium, small) based on typical clinical study designs.

Large study: 100 or more patients studied for 6 months or more

Medium study: 60 or more patients studied for 3 months or more

Small study: 30 or more patients studied for 3 months or more

D. Integration of Premarketing and Postmarketing Studies

ICD development and approval involves evidence of safety and effectiveness gathered during preclinical, pre-approval clinical, and postmarket surveillance studies. The approval of the beginning of human investigation (IDE approval) and the approval for commercial sale (PMA or PMA supplement approval) are simply two points on the development time-line.

The agency is committed to integrating these premarketing and postmarketing activities. The agency is thus supportive of development plans which include earlier introduction into clinical studies and earlier PMA approval, provided such development plans are rational, safe, and provide the necessary clinical evidence. This includes PMA supplements with adequate preclinical data and appropriate postmarketing studies which could be approved without premarketing clinical studies.

Greater specificity and predictability for the clinical study requirements is one of the primary goals of this guidance. Although there are many possible assumptions and designs, the anticipated ICD changes, both evolutional and novel issues, can be reasonably well defined. In particular, for a given specific ICD, Indication, and clinical claim (equivalence or superiority), an appropriate design can be determined.

Table 2 (Appendix G) contains a number of specific designs for specific indications. The associated study design work sheets (one for the premarket study and one for postmarket study) illustrate the approach to developing these specific suggestions.

E. Abbreviations

Abbreviations used in this guidance include:

ATP - Anti-tachyarrhythmia pacing

CAD - Coronary Artery Disease

CDRH - Center for Devices and Radiological Health

EF - Ejection Fraction, Percentage of left ventricular volume that is ejected during systole.

EMC - Electromagnetic Compatibility

EMI - Electromagnetic Interference

EOL - End of Life indication of battery depletion. The device may no longer be able to deliver therapy as a result of battery depletion.

EOS - End of Service indication of battery depletion. Performance may be out of specification below EOS.

ERI - Elective Replacement Indicator. The indicator (typically battery voltage or charge time) that determines when pulse generator needs replacement.

ERT - Elective Replacement Time. The time at which a pulse generator should be replaced based on the ERI.

FDA - Food and Drug Administration (the agency)

FMECA - Failure modes and effects of criticality analysis. Reliability analyses intended to identify failures at the component level which could have significant impact on overall system performance.

GEE - Generalized Estimating Equations, a statistical approach to developing statistical models and estimators.

GMP - Good Manufacturing Practices

HAZOP - Operational hazard analysis. The study of the hazards which might arise as a result of use of the system including the user interface with the device.

HIMA - Health Industry Manufacturers Association

ICD - Implantable cardioverter defibrillator

IDE - Investigational device exemption, permission to begin research involving humans

IRB - Institutional Review Board

J - Joule, Fundamental metric-system unit of energy. A joule is a unit of power equivalent to one watt-second. Most ICDs approved to date deliver a maximum 24-30 J shock.

LVEF - Left ventricular ejection fraction (an important measure of the heart's mechanical function as a pump).

MVT - Monomorphic ventricular tachycardia, ventricular tachycardia with stable morphology of the QRS complexes in at least three simultaneously recorded ECG leads with constant relationship of inscription of the QRS in the three recorded leads.

NASPE - North American Society for Pacing and Electrophysiology

NYHA - New York Heart Association Classification; A commonly used classification of cardiac status and prognosis from class I (uncompromised, good), class II (slightly compromised, good with therapy), class III (moderately compromised, fair with therapy, and class IV (severely compromised, guarded despite therapy)

OUS - Information, usually clinical data, obtained from studies conducted outside the United States

PMA - Premarket Approval application, request for permission to begin commercial distribution.

PMAS - Premarket Approval supplement application, request for a change to the PMA. Changes range from minor manufacturing or labeling changes to major product modifications.

PVT - Polymorphic Ventricular Tachycardia, Ventricular tachycardia with an unstable (varying) QRS-complex morphology in any recorded ECG lead.

RCT - Randomized clinical trial, a clinical study with random assignment of treatment to two or more concurrent patient groups.

REML - Restricted Maximum Likelihood, a statistical approach to assessing mixed models

RPS - Required Postmarket Surveillance Studies -- mandated by the Safe Medical Devices Act of 1990; section 522 of the Federal Food, Drug, and Cosmetic Act

SAS - Statistical Analysis Software; a widely used analysis package from SAS Institute, Inc; Box 8000, SAS Circle, Cary, NC 27512-8000, phone 919-677-8008

SCD - Sudden Cardiac Death; death within one hour after onset of acute symptoms, or worsening of previous stable symptoms. Unwitnessed death, which is unexpected and without apparent cause is also considered a sudden death.

SD - Standard deviation

SE (or SEM) - Standard error, usually SEM (standard error of the mean) = Std Dev / sqrt(N)

SSED - Summary of Safety and Effectiveness Data

VF - Ventricular Fibrillation, Abnormally rapid, irregular rhythm resulting from chaotic electrical activity within the ventricle with absence of clearly defined QRS complexes in the body surface ECG.

VT - Ventricular tachycardia, Abnormally rapid rhythm with aberrant ventricular excitation of the heart characterized by at least three (3) consecutive ventricular complexes of more than 100 beats per minute.

II. Preclinical Testing

Perform *in vitro* ICD testing to ensure that the design, physical characteristics, and integrity of the device are scientifically sound and acceptable for its intended use.

A. Bench Testing

Test all components and the finished device for design verification to specifications by the manufacturer/supplier.

1. Components, Subassemblies and Completed Circuits

Document the test plan for components and subassemblies, including tolerances and limits compatible with the entire system specifications. Identify critical components, with operational and environmental tests designed to verify component reliability. Test for conformance to design specifications, components and/or subassemblies, visual inspection, temperature shock and cycling, solderability, electrical leakage, etc., as appropriate. Perform functional testing before and after environmental and operational stresses.

Perform tests on completed circuits to ensure that the manufacturing process does not compromise component reliability, including: accelerated life tests, mechanical shock and vibration tests, evaluation of bias voltages, temperature shock and cycling, etc., as appropriate.

Environmental Considerations: Since the components of an implanted defibrillator are hermetically sealed, they are subjected to a limited temperature and mechanical range; the environment in which they must function is benign. However, threats such as moisture which can damage material through chemical interaction should be considered. Storage, shipping, and handling before assembly may subject components to excess stresses. When designing components and the finished device, take into consideration the physical environment to which they are exposed throughout the production process.

2. Batteries

Qualification testing should evaluate the suitability and performance of the battery for the particular ICD. The tests should assess the characteristics and general reliability of the components when subjected to stresses anticipated under normal usage, and "worst case" condition.

Testing should include:

a. Electrical Parameters - which verify the component meets design specifications, track parameter drift, component failure, forced discharge and abusive testing, etc.

b. Temperature Challenge - includes high/low temperature storage, thermal shock, temperature cycling, etc.

c. Mechanical Parameter - verify the component meets physical dimension specifications, inspect for defects or damage, verify that materials, construction, and workmanship are in accordance with specifications, etc.

d. Mechanical Analyses - test Hermiticity (seal integrity), Battery Feed-Through, etc.

e. Destructive Analysis - such as Short Circuit Testing at 37° C

f. Operating Life - this involves both accelerated testing and actual life testing which should be ongoing and monitored.

g. Microcalorimetry Testing

h. Longevity Modeling

Report of the testing should include the test procedures, data, and a summary of the results. The test procedures should include the test method, objective, equipment used, test specifications, standards to which conformance is demonstrated, pass/fail criteria, etc. The summary of the results should include an analysis explaining the significance of the results.

3. Capacitors

The high-voltage capacitors should be subjected to both accelerated and real-time testing by the manufacturer/vendor. Document the test plan, including tolerances and limits compatible with the entire system specifications. Parameters such as capacitance, charge time, and electrical leakage should be measured pre- and post-testing. Note any change in visual aspect from testing.

a. Electrical Parameters - which verify the component meets design specifications, track parameter drift, components failure, forced discharge and abusive testing, etc.

b. Charge/Discharge cycling - design a test to determine the life cycle of a capacitor using the following protocol to simulate intermittent usage:

   i. Starting with an uncharged capacitor, measure the time needed to charge the capacitor to the rated voltage using a specified current. Note that this time also determines the rate of capacitor reformation.

   ii. Measure the duration the capacitor can hold a specified percentage of the rated voltage without additional charge (leakage rate).

   iii. Charge the capacitor back to the rated voltage and rapidly discharge the capacitor through a resistor.

iv. Repeat steps i through iii two more times to simulate consecutive shocks from the capacitor during one arrhythmia episode.

v. Record the duration the capacitor remains uncharged after step iv.

vi. Repeat steps i through v. Stop when the charge time in step a increases by more than a specified percentage of the initial value. Alternatively, stop when the duration measured in step ii decreases by more than a specified percentage of the initial value.

c. Surge Voltage - determine that the capacitor can withstand over voltage conditions

d. Shelf Life

e. Destructive Analysis

f. Mechanical Parameters - verify that components meet physical dimension specifications, inspect for defects or damage, verify that materials, construction, and workmanship are in accordance with specifications, etc.

g. Mechanical Analyses - test characteristics such as termination strength, solderability, etc.

h. Operating Life - this involves both accelerated testing and actual life testing which should be ongoing and monitored. The results from the accelerated life test data can be compared to real-time data.

Report of the testing should include the test procedures, data, and a summary of the results. The test procedures should include the test method, objective, equipment used, test specifications, standards to which conformance is demonstrated, pass/fail criteria, etc. The summary of the results should include an analysis explaining the significance of the results.

4. Leads

Whether part of a thoracotomy or non-thoracotomy system, all lead components should be subjected to testing and evaluation. The following series of non-clinical tests are intended to establish minimum requirements considered appropriate to qualify a "new" defibrillation lead system or components thereof. Sponsors should examine this listing to determine testing appropriate for their device. For example, if a currently marketed lead is being slightly modified, only data needed to qualify that change need be provided.

New lead designs may result in failure modes previously unseen and, therefore, not reflected in this document. It is the responsibility of the sponsor to define a comprehensive testing methodology for a particular lead design.

a. Biocompatibility: (see Section II.C for guidance on biocompatibility)

b. Animal Studies (see also section 9.D for more information and guidance on animal studies)

The purpose of animal studies is to assess the electrical performance, mechanical performance and biostability of the fully assembled leads. Animal studies should be designed to closely approximate the intended use of the device in humans, including evaluation with the model(s)of implantable defibrillator to be used with the lead. In addition, representative lead configurations and pulse pathways should be evaluated. Generally, the canine model is considered adequate to evaluate defibrillator leads, although it may be difficult to evaluate patch leads in this model. A sufficient number of animals/leads should be implanted so that valid conclusions may be drawn.

Electrical data should consist of the measurement of the following parameters:

i. - defibrillation thresholds (DFTs);

ii. - pacing and sensing thresholds at baseline and post-shock;

iii. - impedance; and

iv. - energy delivered/shock

Possible dislodgements and/or migrations should be documented by radiography and suspected infections should be cultured and identified. Fluoroscopy should be used to evaluate lead movement during shock delivery. The ease of implant and overall handling characteristics of the lead should be noted for each implant.

A report should be given for each animal, describing its pre-operative condition and providing general information such as lead handling characteristics and surgical techniques used, as well as a summary of all postmortem findings.

At explant, the heart should be excised intact and examined via necroscopy and histopathological analysis for evidence of shock-induced damage to the myocardial tissue resulting from multiple high-energy defibrillation shocks. Possible complications resulting from the use of patch leads (if applicable) should be noted, e.g. erosion, hematomas, tumor growth, etc.

Leads should be removed intact and examined for structural integrity and biostability. Biostability of the insulator should be documented by using a state-of-the-art analytical technique(s) such as SEM, IR, molecular weight, stress- strain, etc.

In addition to the tests noted above, steroid-eluting leads should be tested in animals with a steroid-free control lead, as appropriate, to establish threshold and sensing improvements as well as comparative fibrous tissue encapsulation. The residual steroid level remaining in the leads should be made after sacrifice of the animals.

c. Electrical and Mechanical Performance Testing

Testing should be conducted on components, subassemblies and/or finished leads, as appropriate. All tests should be performed on leads fabricated by representative manufacturing processes and subjected to the final validated sterilization procedures intended for the device.

An adequate number of samples, based on relevant power calculations should be tested. If sample devices of different lead models are not tested, it should be clearly indicated which models were used for each test. The absence of testing on each model should be justified by an analysis demonstrating that the results from the tested devices will accurately predict results for the untested device models.

For any tests that result in device failure, the failure mode should be completely described. The significance of any tests that result in failure of the lead or subassembly to meet specification should be discussed. Corrective actions taken to eliminate or minimize further occurrence of failure should be evaluated via retesting of modified samples.

The performance specifications for all components, subassemblies, and finished devices, and test conditions and acceptance criteria for all tests should be completely, explained and justified by comparison to expected *in vivo* conditions. Where appropriate, testing should be conducted in an environment simulating *in vivo* conditions. The results of all tests should be reported in a statistically meaningful format, i.e., specification of the number of samples, range of values, mean, standard deviation, and a 95 percent confidence interval where appropriate. A probability

measure that is indicative of the statistical significance of any comparisons made should be provided.

Electrical continuity and isolation and mechanical integrity of sterilized leads or subassemblies should be evaluated following thermal cycling. Testing should include, but are not necessarily limited to, the following, as appropriate:

i. Verify the electrical continuity of each conduction path by measuring the DC resistance. These measurements should comply with the manufacturer's specifications.

ii. Measure leakage current during voltage application. ISO/DIS 11318 describes an appropriate testing methodology.

iii. Evaluate the ability of the lead to deliver high energy pulses in a testing model that simulates the resistances of the heart and thorax. In addition evaluate the lead's ability to withstand crush forces following application of high energy voltage.

iv. Determine the strength of each bond, joint, etc. in the lead (lower 95 percent confidence bound). Leads should be subjected to a tensile force which simulates the stress it may experience during the implant procedure as well as after implant. The lead should be soaked to introduce any effects of body fluids on the lead joints and body.

v. Test for integrity of all joints, bonds, etc. by conducting a leak test in isotonic saline at 37° under physiological pressure for a minimum period of ten days.

vi. Document the corrosion resistance of all conductors and electrode materials when subjected to high energy shocks.

vii. Evaluate the performance of the stylet intended to be used during lead placement. Measure the stylet removal and insertion forces as well as the torquability of the stylet.

viii. Fatigue resistance of the conductor(s) should be verified. Whole, intact leads should be used for this testing, and the testing should be conducted following multiple high energy pulsing in a simulated saline environment. Loading conditions that are utilized should be able to be extrapolated to worst-case physiological conditions, i.e., ranges of motion, stresses, etc. Different areas of the lead are subjected to different stresses; this factor should be taken into consideration in the design of an appropriate test protocol. Test methods designed to accelerate fatigue of conductors should be shown to be able to produce characteristic fracture morphologies in vivo.

ix. Connectors intended to be used for joining implantable defibrillators and leads should withstand the mechanical forces that might occur during connection to the defibrillator as well as after implantation. Insertion/withdrawal forces should be measured to ensure compatibility. Generally, most defibrillator lead connectors are designed to comply with ISO 11318 (DF-1). This standard outlines the appropriate testing for lead connectors. If a connector is labeled as "DF-1" compatible, all dimensions should be compatible with ISO 11318.

x. Life tests (real-time testing) should be performed on new defibrillation leads prior to approval for marketing. An on-going life test protocol should be developed and submitted for review prior to its implementation. Periodic reports on life-testing of the leads should be provided to FDA while the testing is on-going. The results of life-testing will allow for the prediction of reliability for all system components (including the lead).

xi. Lead stiffness should be measured to determine the pressure exerted by the lead tip. Measured values should be compared to a lead with previous clinical experience.

xii. Measure the force required to securely suture an anchoring sleeve on a lead body. After suturing, verify the integrity of the insulation and conductor coil(s) via microscopic evaluation.

xiii. For steroid-eluting leads, in vitro elution rate should be quantified. Distal subassemblies containing the drug eluting component should be immersed in an appropriate medium and analyzed at periodic intervals. The amount of steroid eluted over time should be quantified. Aged steroid leads should be analyzed to determine whether the drug composition/quantity varies over the proposed shelf life of the product. In addition, the polymer matrix used to house the steroid should be examined for swelling and/or degradation over time.

The finished device or system, including the leads, represents the intended marketable product. Areas concerning device function should be addressed by this stage of testing. The protocol for testing the finished device and the pass/fail criteria for each test procedure should be described. Each test should be conducted in accordance with established standards or procedures. The tests include the following:

5. Electrical Characterization of the Finished Device

This testing should be designed to verify the function of the ICD system within specified tolerances in the human body during the device's expected operational life. All parameters such as rate, pulse amplitude, pulse width, sensitivity, and timing cycles and periods, and all features such as intracardiac electrograms, remote measurements, hysteresis, and elective replacement indicators, should be characterized for functioning under expected temperatures (30•C to 40•C), loads (300 ohms to 2000 ohms), and battery voltage (beginning of life (BOL) to end of service (EOS)). The device shall be programmed to each mode and feature, and to the lowest, nominal, and highest values of programmed parameters. Use immersion techniques in physiological solution to adequately simulate clinical conditions as appropriate.

6. Environmental Testing

The ICD system should be subjected to mechanical and environmental tests to assure that the device will meet its labeled specifications; the conditions should exceed those normally seen in handling, shipping, storage, or clinical use. Depending upon device design and types of environmental stress reasonably expected, types of tests may include electromagnetic, electrical, magnetic, mechanical, thermal, acoustic, or chemical interference.

These test shall include:

- temperature storage or cycling tests,
- mechanical vibration tests, and
- mechanical shock tests.

7. Electromagnetic Compatibility (EMC)

The ICD *system* should be evaluated for its susceptibility to external sources of electromagnetic interference (EMI). Evaluate for susceptibility as a *pre-implant system* (device, leads, external device, patient cables) if used in the intraoperative procedure; otherwise, evaluate for normal operation as an *implant system* (device and leads).

EMI is ubiquitous and generated from many sources. They can be induced from the general environment, the clinical setting, occupational environments, the human anatomy, and other implanted devices. The effects of interference on the device operation such as its detection and

therapeutic functions, memory, device-programmed selections and diagnostic capabilities should be fully characterized.

Perform EMC testing in various orientations and exposed to appropriate field strengths and range of frequencies represented by the different environments. Describe the test methods, acceptance pass/fail criteria, and summary of results with proper references to voluntary standards used in testing the ICD system.

Evaluate the following sources of interference for all devices as appropriate to the specific device design:

- conducted and radiated electromagnetic fields,
- digital cellular telephone systems,
- electronic article surveillance systems (security, anti-theft),
- electrosurgical units, and
- external defibrillation,.

Include in the device labeling appropriate warnings concerning other environments capable of producing electromagnetic fields that can interfere with proper device operation such as arc welding equipment, radio, television, slot machines, radar transmitters, power-generating facilities, etc.

Analyze the results from testing the device for standards of electromagnetic immunity and emission to assure that the ICD system meets or exceeds specifications and device labeling. Summarize sources and possible effects of EMI interaction with recommendations on how to minimize its effects in the physician and patient manuals.

8. Programmers and External Testers

Equipment built for verification testing of an ICD device interrogation should be representative of marketable products, and subjected to functional, environmental, interference, software, and reliability testing. This testing should be designed to assure its operation according to written specifications in conjunction with any and all of its intended pulse generators, under specified, expected environmental conditions. Survival in use as well as in storage, shipping, and handling, should be characterized for all portions of the programmer/external tester system.

The tests on the finished units should be designed so that data are generated which support and document the proper functioning of the system. The data should show that the system performs to specifications. The protocol of testing and the pass/fail criteria for each test procedure should be described. Each test performed should be done in accordance to established standards or procedures.

9. Device Reliability

Any specific reliability performance claims in the labeling or promotional literature for ICD devices should be supported in the application to FDA. Supporting data should include, but need not limited to, detailed definitions of all types of failures (e.g., catastrophic, critical, major, minor), a Failure Modes, Effects, and Criticality Analysis (FMECA), reliability predictions and models (with prediction data sources identified), identification of all failures that occurred in all component or finished device testing and the corrective action taken to preclude subsequent failures, and the actual calculations used to determine the device reliability. Complete description of the reliability analysis tool(s) used should be provided. Reliability claims, if made, should be in the form of a specified reliability at a specified duration of use with one-sided confidence intervals (minimum 60%).